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Effect of gender, body mass index, albumin and normalized protein catabolic rate on erythropoietin responsiveness in maintenance haemodialysis patients

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Abstract— Background: Chronic kidney disease (CKD) cases frequently experienced anaemia because of iron restriction and inflammation.Iron supplements, erythropoiesis-stimulating agents (ESAs) and, in extreme circumstances, red blood cell transfusions are options being used to treat anaemia caused by chronic kidney disease. **Objective:** to investigate the relationships between ESA resistance and gender, BMI, albumin, and the normalised protein catabolic rate. **Methodology:**Over the course of more than three months, ninty seven patients aged eighteen to seventy five who have been receiving steady haemodialysis treatment at the haemodialysis unit at Theodor bilharz research institute (TBRI).The medical histories as well as physical examinations of all patients were thoroughly documented, down to the patient's age, gender, race, whether or not they had received EPO, and the patient's EPO dosage in units per week.Weight and height were assessed as well as BMI was determined as weight/height (kg/m2). **Results:**Our data showed that the mean ERI was 14.8 U/kg/week EPO/Hb g/dL, that there was no link between ERI and gender, ERI and urea levels showed negative correlation before and after dialysis ($p= 0.013$), creatinine levels ($p= 0.002$), BMI ($p= 0.016$), and N-PCR ($p= 0.034$)and highly statistically negative correlation between ERI and haemoglobin level($p<0.001$)and serum albumin($p<0.001$),ERI and CRP showed highly statistically positive correlation($p<0.001$). **Conclusion:**EPO hypo-responsiveness was associated with body mass index (BMI), serum albumin, normalised protein catabolic rate and C reactive protein according to our research. Gender did not play a role in EPO responsiveness.

Keywords: EPO hypo-responsiveness, BMI, albumin, N-PCR and hemodialysis.

Introduction:

Several clinical studies focus on the anemia management and malnutrition in chronic kidney disease (CKD) cases with the goal of enhancing the survival as well as quality of life among of CKD subjects because of their importance as a major risk factors of morbidity and death in ESRD patients. (1), (2).

Management of anaemia in CKD patients typically involves the administration of erythropoiesis-stimulating agents (ESA), but many studies have shown a link between higher doses of recombinant human erythropoietin (EPO) and mortality. Thus, researchers have carried out plenty of investigations over the past decade to better comprehend the factors that contribute to EPO's effectiveness and the optimal dosages. (3), (4).

Due to the intricacy of factors influencing recombinant human erythropoietin (EPO) response in CKD cases, the erythropoietin resistance index (ERI) calculation is a crucial tool for assessing how well a patient will respond to erythropoietin-stimulating agent (ESA)(5).

Chronic kidney disease cases have a wide range of responses to erythropoietin (EPO), and this range can be altered with the use of the erythropoietin resistance index (ERI), which is a very straightforward method for measuring this response. (6). Sensitivity of the ERI allows for reliable recognition of initial deviations (7).

Independent researches have shown that factors like low parameters of body mass index (BMI), albumin level (albumin concentration in the blood), malnutrition, inflammation, iron deficiency status (IDS), increased levels of parathyroid hormone (PTH), and the utilization of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) which all contribute to increased ERI. (6).

There is evidence that BMI influences response of the body to ESA, although it remains unclear whether or not BMI is alone or largely responsible for the observed shift in ERI. (8).

Materials and methods:

Study design:

This retrospective cross-sectional study examined persons aged from eighteen to seventy five who have been receiving haemodialysis treatment at Theodor bilharz research institute (TBRI), Giza, Egypt, on a regular basis for more than three months and are in stable condition due to end stage renal disease.

Cases have severe cerebrovascular or cardiovascular diseases, any infectious diseases within one month, malignancy, active liver disease, recent surgical procedures or blood transfusion, active haemorrhage; pure red cell aplasia and patients not use EPO were excluded from this research.

All procedures were performed in compliance with the principles established in the Declaration of Helsinki and its later amendments, and all patients provided signed informed consent before enrolment in the study.

Information such as demographics, EPO administration, and EPO dosage (in units per week) were recorded. Body mass index (BMI) was determined by dividing their total body weight by their squared height in metres.

All trial peoples began haemodialysis at a blood flow rate of 250–300 mL/min and a bicarbonate dialysate flow rate of 500 mL/min. The membrane's size in the dialyzer was based on the patient's body mass. Dialysate has a nutrient profile that includes glucose (100 mg/dL), calcium (1.25%), magnesium (0.5%), and potassium (2.0%). Two thousand six hundred to five thousand international units of heparin were given per four-hour HD session for anticoagulation purposes.We used the patient's clinical dry weight to determine the UF volume for each session.

Blood tests:

Haemoglobin, ferritin, transferrin saturation ratio, Calcium, phosphorus, Intact PTH (iPTH) level,renal Function Tests {creatinine, urea (pre and post dialysis)}, albumin and dialysis adequacy (URR, KT/V) were performed to all participants in theresearch.

For the purposes of this study, ERI was calculated as follows: ESA dose in (units) per week / clinical dry weight in (kg) / haemoglobin in (g/dL).

Normalized protein catabolic rate (n PCR) is a calculation commonly used in haemodialysis patients to determine the dietary protein intake and used as a tool to assess nutritional adequacy in dialysis patients and werecalculated by the following equation:

N pcr (g/kg/day) =C0/ (a+bkt/v+c/{kt/v}+0.0168

Dialysis dose is calculated by urea reduction ratio (URR) meaning the reduction in urea as a result of dialysis. The URR is usually measured only once every 12 to 14 treatments, which is once a month. Calculated as URR=100%×(pre dialysis BUN−post dialysis BUN)/pre dialysis BUN.

kt/v is the single-pool estimate of the dialysis dose.

Statistical analysis:
SPSS version 24 was used for all statistical analysis (SPSSInc, IL, USA).Mean and standard deviation were used to summarize the quantitative data, while the qualitative data was summarised using frequencies and percentages. To check for statistical significance between two set of data, we employed the Student t test. One-way ANOVA and Turkey's test were appliedin order to look for statistically significant differences between the groups. As a quantitative cut-off for significance, the value of 0.05 was used.

Results:
End-stage renal disease (ESRD) cases whohad undergone maintenance HD were included in this clinical investigation; their personal information and health records are contained in (Table 1).

Table (1) baseline data among patients

Table (1) Distribution of patients according to baseline data

	Mean ± SD/median	Range/IQR
BMI (kg/m2)	25.79 ±6.58	12.4 – 43
Age (year)	46.57 ± 15.17	15 – 75
Male gender	51§	52.6%
Female gender	46§	47.4%

Urea pre-dialysis (mg/dl)	61.07 ± 18.51	8 – 104
Urea post-dialysis (mg/dl)	18.25± 12.62	3- 95
Creatinine (mg/dl)	9.38 ± 3.11	2.88 – 18.63
Haemoglobin (g/dl)	11.1 ± 1.4	7.9 – 14.1
Transferrin saturation (%)	34§	27 – 41
Ferritin (µg/ml)	538.5§	357.95 – 811.4
Albumin (mg/dl)	3.86 ± 0.37	2.5 – 4.8
CRP (mg/dl)	16.59±15.04	6-78
N-PCR (g/kg/day)	1.3 ± 0.29	0.6 – 2.9
Calcium (mg/dl)	8.8 ± 0.87	5.9 – 10.6
phosphorus (mg/dl)	5.58 ± 1.78	1.7 – 10.2
PTH (pg/ml)	527.1§	322.05 – 743.6
URR	72.6 ± 9.01	45.2 – 92.5
Kt/VD	1.62 ± 0.44	0.72 – 3.3
ERI	14.8§	8.74 – 21.24

Not normally distributed data is represented as median and interquartile range(IQR), SD: standard deviation, BMI: body mass index, CRP: C-reactive protein, N-PCR: normalized protein catabolic rate, PTH: parathyroid hormone, URR: urea reduction ratio, ERI; erythropoietin resistance index.

Female HD cases had an ERI of 16.41 (9.03 - 26.45) and male HD cases had an ERI of 12.65 (8.17 - 19.12) (p=0.1; Figure 1). These findings indicated that ERI and gender did not show any statistical significant difference in the studied populations.

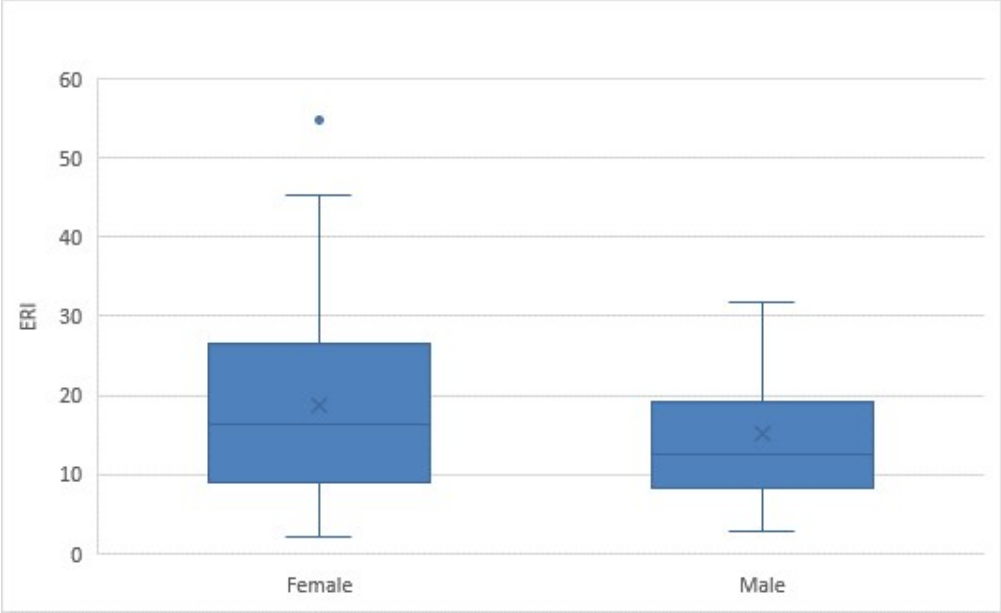

Figure (1) Boxplot showing relation between gender and ERI (median and interquartile range for females were 16.41 (9.03 – 26.45) and 12.65 (8.17 – 19.12) for males (p=0.1)

We found that among the patients we analysed, a substantial inverse association existed between ERI and urea concentration (before dialysis) (r= -0.251, p= 0.013),urea level (after dialysis) (r= -0.201, p= 0.049), creatinine level (r=-0.312, p=0.002), body mass index (r=-0.244, p=0.016) andN-PCR (r=-0.216, p=0.034), ERI and CRP showed highly statistically positive correlation(r=0.564,p<0.001).

ERI is not linked to the other variables (in table 2) in any significant way, and there is a great negative correlation between ERI and haemoglobin (r=-0.708, p0.001) and serum albumin (r=-0.405, p0.001) (figure 2, 3, 4, 5).

Table (2) Correlation between ERI and the studied parameters:

	r	p
BMI (kg/m2)	-0.244	0.016*
Age (year)	0.016	0.878
Urea pre(mg/dl)	-0.251	0.013*
Urea post(mg/dl)	-0.201	0.049*
% change in urea	-0.065	0.528
Creatinine (mg/dl)	-0.312	0.002*

Haemoglobin (g/dl)	-0.708	<0.001**
Transferrin saturation (%)	-0.154	0.131
Ferritin (µg/ml)	0.104	0.311
Albumin (g/dl)	-0.405	<0.001**
CRP	0.564	<0.001**
Calcium (mg/dl)	-0.134	0.189
Phosphorus (mg/dl)	-0.103	0.314
PTH (pg/ml)	-0.049	0.613
Kt/VD	0.056	0.583
N-PCR(g/kg/day)	-0.216	0.034*
URR	0.113	0.272

ERI; erythropoietin resistance index, BMI: body mass index, CRP: C-reactive protein, , PTH: parathyroid hormone, N-PCR: normalized protein catabolic rate,URR: urea reduction ratio.

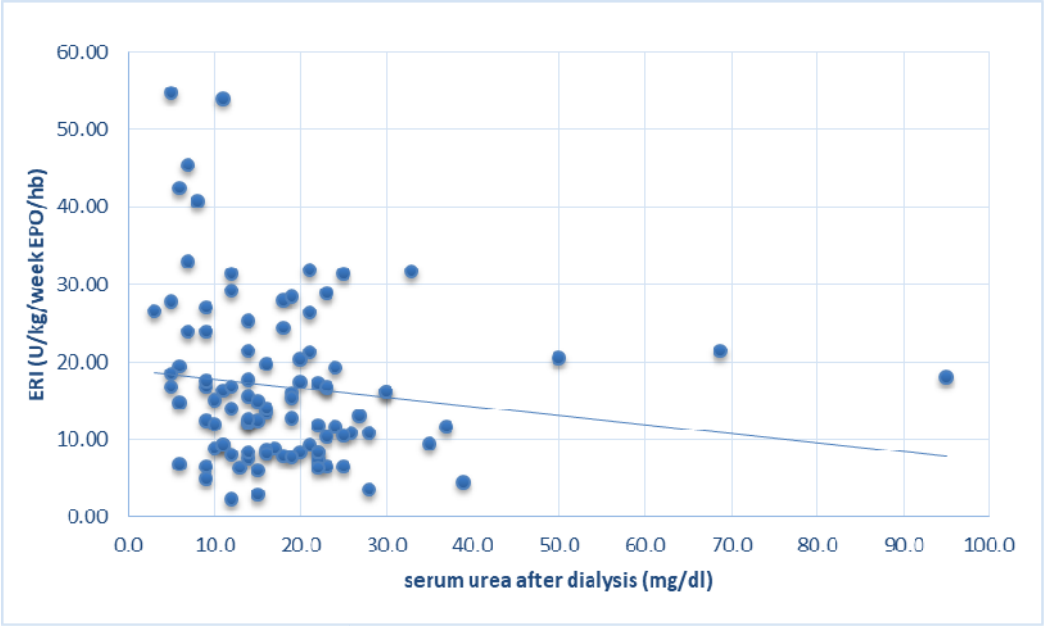

Figure (2) scatter diagram depicting a negative association between (ERI) and serum urea levels in patients on dialysis.

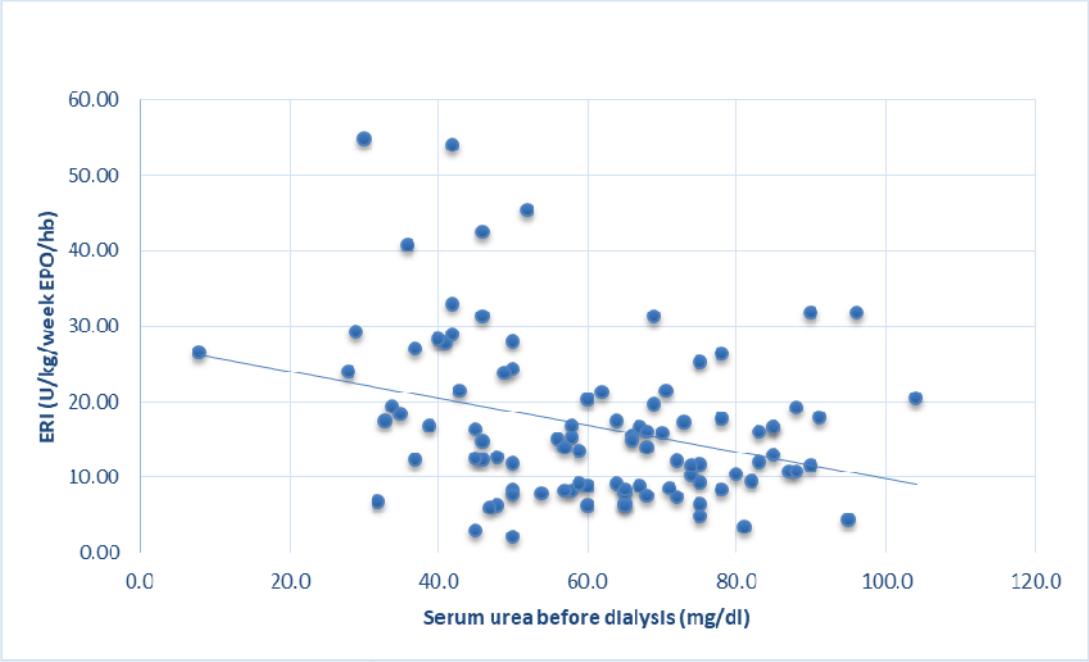

Figure (3) scatter diagram depicting a negative association between ERI and pre-dialysis serum urea.

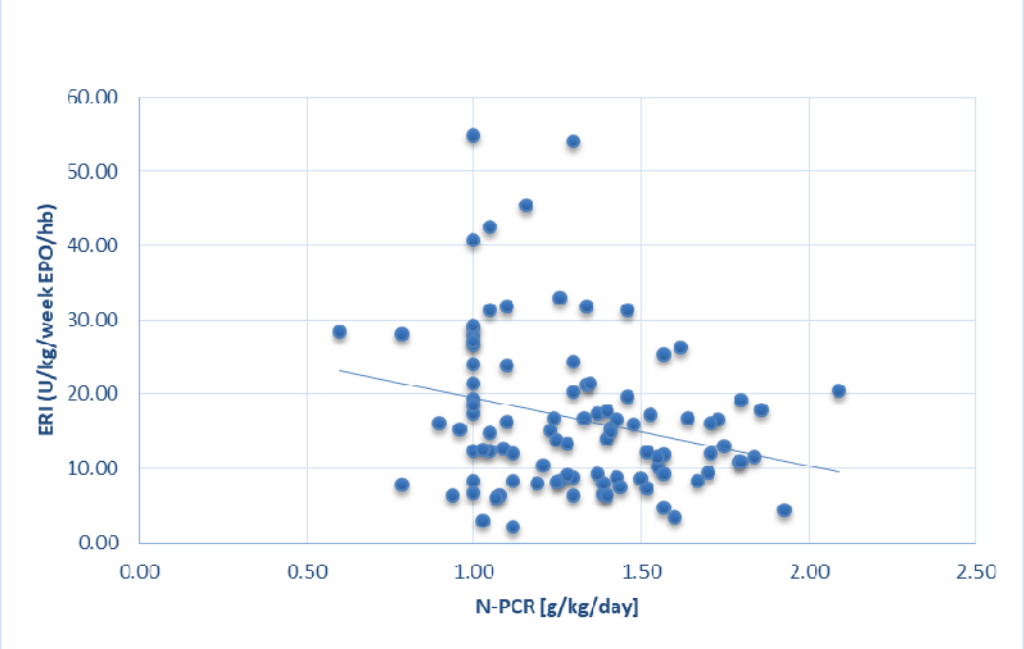

Figure (4) scatter dot graph showing significant negative correlation between ERI and N-PCR.

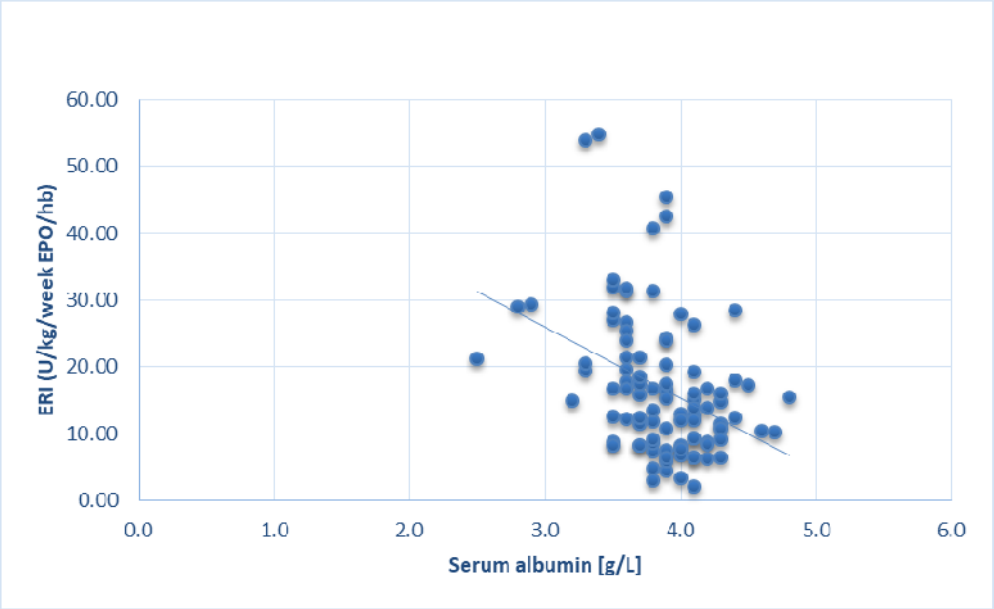

Figure (5) scatter dot graph showing highly significant negative correlation between ERI and serum albumin.

Discussion

Anemia is a common problem in patients who undergo renal replacement therapy due to decrease of erythropoietin (EPO) synthesis by the kidneys, which is considered the main cause of such a state, iron deficiency is happening in HD patients due to persistent blood loss through the dialysis circuit, decrease red blood cell lifespan, recurrent blood collection, and noncompliance with management (9).

In this study, we examined the response to erythropoietin therapy by calculating the ERI using the weekly weight-adjusted dose of αEPO and hemoglobin level.

EPO and intravenous iron were used to treat the anemic cases. Cases with HD can benefit from this treatment plan since it increases hemoglobin to the recommended levels & low complications (10, 11).

In the present study in which a population of CKD patients subjected to HD in TBRI were evaluated, we found a negative association between serum levels of albumin and the ERI (p value 0.001which means that, an increase in serum albumin level of increased the response to EPO, similar to the findings of Juan and collogues (12). This may be explained in part by the fact that a rise in serum albumin is often associated with decreased inflammation and oxidative stress, and an improved nutritional state (5), and hence improvement of the general health. In addition, certain clinical conditions, such as malnutrition and inflammation, disrupt erythropoiesis and result in hypoalbuminemia (13, 14).

However, Kalantar-Zadeh *et al found no correlation among low serum albumin level& either EPO dose or ERI.* These cases were probably better dialyzed and better nourished (15).

In contrast to general population, individuals undergoing renal replacement therapy have a higher mortality risk from malnutrition than from obesity (16, 17). Our aim in this study was to learn more about the relationship between dietary status& erythropoietin sensitivity. In our hemodialyzed patients, we established a negative correlation between BMI and ERI (p 0.016), considered with previous researches (12, 18).

Inflammatory status is relevant to renal patients receiving maintenance hemodialysis since inflammatory state of CKD causes resistance to the medullary action of EPO (7). This is explained by that, post-inflammatory cytokines such as interleukin and tumor necrosis factor, act on the erythropoietic progenitor cells, opposing the actin of EPO and stimulating apoptosis (7, 8).

Dialysis patients frequently had low-grade inflammation because of variety of causes including, oxidative stress, uremia toxin accumulation, metabolic disorder, and other pathological conditions, leading cytokines disorder (19, 20). Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are examples of inflammatory cytokines that may inhibit erythropoiesis. Increased levels of IL-6 and TNF-α have been linked to disruption iron metabolism and reticuloendothelial system iron storage. These cytokines might also cause direct harm to red blood cells and trigger apoptosis in bone marrow (21). The malnutrition-inflammation complex results in incrementally poor responsiveness to EPO (22).

Serum albumin levels not only reflect dietary intake but also acts an inflammatory marker, which acts as a negative acute phase reactant. In this study, the strength of the response to EPO was found to be related to albumin concentration. A drop in albumin level is accompanied by an increase in ERI (p value 0.001). As a result, underlying inflammatory processes should be excluded as the cause of ESA resistance (23).

ESRD cases need regular nutritional monitoring. In the attempt to develop markers to evaluate the nutritional status, various laboratory parameters have been taken into consideration. In stable chronic hemodialysis patients the protein catabolic rate normalized by body weight (nPCR) is periodically determined to evaluate dietary protein consumption (15). Malnutrition is strongly linked to outcome in this population, earlier research had examined nPCR as a nutritional marker & its effects on morbidity and mortality (24).

ESRD cases on maintenance dialysis frequently experience protein-calorie malnutrition, which is key predictor of mortality (25, 26).An increase in nPCR by 0.1g/kg/day is associated with 15% reduction in mortality (24,27). Making nPCR the most important risk factor for mortality.

Our findings suggested that, reduced protein intake was linked to elevated ERI because of the negative correlation between ERI and nPCR On the other hand, Lopez-Gomez et al. (6) discovered a correlation between low values of ERI and albumin levels, but no relation with the normalized protein catabolic rate.

As CRP serves as inflammatory marker, and is predictive of resistance to ESA treatment, so we used it (23). We found that, there was a positive correlation between the CRP and the ERI (p value 0.001), meaning that, higher CRP levels were associated with higher resistance to treatment. The correlation between inflammation & EPO hyporesponsiveness is supported by other findings, which are consistent with those of other researches. This correlation appears to be among cases whose CRP increase was maintained over the subsequent three months (22).

We observed a negative correlation between ERI and BMI ($p = 0.016$), this means that an increased BMI was associated with an improved response to EPO treatment. , in hemodialysis patients, the obesity is associated with a better clinical outcomes than general population (30). The lower the BMI, the larger the uremic toxin load (29).

Previous studies demonstrated that ESA dose requirements and the ERI are inversely related to total adipose tissue in dialysis patients (28, 29).

The BMI is an important nutritional status marker in these patients. Unlike the general population

The URR is a straightforward measurement of urea reduction (%) during a hemodialysis session. In this investigation, there was no correlation between ERI and URR, however, Santos et al discovered that, higher URR was associated with a better response to EPO medication for anemia (31). High URR may indicate a successful dialysis session, which is typically associated with an enhanced response to ESA medication (32, 33)

Serum ferritin is a measurement of iron storage in the liver &reticulo-endothelial system (RES) as well as being an acute phase protein, therefore, the elevated ferritin level in hemodialysis patients can't be entirely explained by inflammation &requires additional investigations (34).

In those patients undergoing regular HD, having elevated serum ferritin levels were at risk for development of EPO resistance (21). In contrast, our data revealed no link between ERI and serum ferritin, however, other studies identified a strong positive correlation between the ERI and serum ferritin concentration (20, 21).

We discovered no link between ERI and transferring saturation, however, other research have demonstrated that transferrin saturation is higher in EPO sensitive group than in EPO resistant group (34).

Hyperparathyroidism is a predictor of hyporesponsiveness to EPO (35, 36), in this investigation, there was no connection between intact PTH & ERI. According to a number of studies, uremic individuals with severe renal anemia showed considerable improved post parathyroidectomy (36, 37).

Some investigators in contrast, found no association between hyperparathyroidism and ERI (38, 39). Some authors noted that patients with relative hypoparathyroidism respond better to treatment (40). Excess PTH secretion results fibrosis in bone marrow and concomitant

defective erythropoiesis (41). Overall, PTH does not directly impede human erythropoiesis; instead, bone marrow fibrosis and the uremic milieu are responsible for EPO hyporesponsiveness (42).

Kt/V ratio, a dimensionless measure of urea elimination during a single RRT procedure, is most often indicator of dialysis adequacy. In this ratio, K represents the volume of blood that goes through the dialyzer milliliters per minute. K is particular to the model of the dialyzer. *t*, represents the dialysis period in minutes, and V represents the urea volume distribution in the denominator. In common practice, it is assumed that the higher levels of Kt/V, dialysis is more effective. Yet, it is important to remember that, that urea is not the only toxic molecule that must be removed during dialysis (18)

Some authors have shown that lower Kt/V values are associated with higher doses of EPO (26, 27). Our results do not confirm it, although it is important to note that mean spKT/V in our patients was high and only few patients had lower levels of spKT/V than those currently recommended(44,43).

The effect of the dialysis dose may have been hidden within the typical range of values in our patients. Online hemodiafiltration and high convective transport methods have been linked to reduce EPO needs (29, 30).

Recently, there have been many investigators suggested that Kt/V is no longer a valid indicator of dialysis adequacy, because it fails to account individual patient characteristics (e.g., “other-than-average” body composition) and other uremic solutes into account (44,45,46). Other uremic toxins should be considered (such as beta-2-microglobulin, IL-6, indoxylsulfate, *p*-cresylsulfate, etc.) and not urea alone, accounts for dysregulation of erythropoiesis and the worsening of malnutrition through a wide range of mechanisms beyond the scope of this publication (46, 47)

Female HD patients had an ERI of 16.41 (9.03 - 26.45) and male HD patients had an ERI of 12.65 (8.17 - 19.12) (p=0.1; Figure 1). These results indicated that ERI and gender did not show any statistically significant difference in the analyzed populations. Although another study detected hyporesponsiveness in women who needed higher dose of EPO than men to achieve a hematocrit target (48).

Study limitations

A limitation of our study is that we did not investigate other nutritional deficiencies, which can affect the synthesis red blood cells, such as vitamin B12 and folate. Bleeding episodes may have occurred. Furthermore, we did not investigate hemoglobinopathies and other hereditary red blood cell abnormalities, which could cause refractory anemia. We did not record other comorbidities such as malabsorption. Additionally, we did not record other diseases, which can cause anemia of chronic disease such as autoimmune diseases and hypothyroidism.

Conclusion

Our data showed that, patients on maintenance haemodialysis who had a lower body mass index (BMI), lower serum albumin levels, lower normalised protein catabolic rate and high C reactive protein were more likely to be EPO hypo-responsive causing a rise in ERI. Because of the cross-sectional nature of this trial and its single-centre setting, our findings may not be applied to other populations requiring HD maintenance therapy.

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Conflicts of interest
there are no conflicts of interest.

Ethical considerations concerning unethical practises (such as plagiarism, data manipulation, and double publication), the authors have followed thoroughly Funding/Support none of the companies involved in this study provided funding for it.

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